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Jeune Syndrome With Tongue Lobulation and Preaxial Polydactyly, and Jeune Syndrome With Situs Inversus and Asplenia: Compound Heterozygosity Jeune-Mohr and Jeune-Ivemark?

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We report on a male infant with internal hydrocephalus, absence of corpus callosum, papillomas and lobulation of the tongue, notches of the alveolar ridges, short ribs, dysplastic pelvis, hypospadias, short limbs with bowed long tubular bones and postaxial polydactyly of hands, and preaxial polydactyly in one foot. Radiologically this case shares manifestations with Jeune syndrome; the tongue lobulation and the preaxial polydactyly are similar to findings in Mohr syndrome, or short-rib polydactyly syndrome (SRPS), type Majewski. In addition, a female newborn presented with manifestations of Jeune and Ivemark syndromes. One explanation for this overlap may be compound heterozygosity for these syndromes. © 1996 Wiley-Liss, Inc.

KEY WORDS: Jeune syndrome, Mohr syndrome, short-rib polydactyly syndrome, Ivemark syndrome, compound heterozygosity

INTRODUCTION

There are at least six short-rib (-polydactyly) syndromes (SRPS) [Beighton et al., 1992], and 8–11 orofacio-digital (OFD) syndromes [Münke et al., 1990; Gurrieri et al., 1992; Figuera et al., 1993; Gabrielli et al., 1994] that seem to be clinically distinguishable. Beighton et al. [1992] classified the short-rib dysplasias with or without polydactyly into SR(P) type I (Saldino-Noonan), type II (Majewski), type III (Verma-Naumoff), type IV (Beemer-Langer), Jeune syndrome, and Ellis-van Creveld syndrome (Table I). Toriello [1992] divided the OFD syndromes into at least nine types (Table II). The debate over whether these classifications are correct is unresolved, especially since there are a number of cases with manifestations of more than one syndrome.

We report on two newborns, one with signs of Jeune, Mohr, and Majewski syndromes, and the other of Jeune and Ivemark syndromes. We discuss compound heterozygosity due to allelic mutations as the possible cause for the overlapping cases reported so far.

CLINICAL REPORTS

Case I, a boy, was born in 1989 as the second child of healthy and nonconsanguineous Turkish parents. At birth, the mother was 28 and the father 31 years old. Two younger sisters are healthy. He was born at 39 weeks gestation, birth weight was 2,630 g, length was 47 cm, and occipitofrontal circumference (OFC) was 35 cm. Apgar scores were 7, 8, 8, at 3, 5, and 10 min, respectively. Despite assisted ventilation the infant was cyanotic. He had an abnormal face with hypertelorism, broad tip of nose, and retrogenia. The upper and lower alveolar ridges were irregular due to multiple notches. The tip of the tongue was lobulated (Fig. 1), and there were some white papillomas on the tongue, 2–3 mm in diameter. The neck was short and the thoracic cage was long and narrow, with mild pectus excavatum. Spleen and liver were enlarged; the abdomen was protuberant. There was a short penis with hypospadias and a bifid scrotum, and bilateral cryptorchidism. The limbs were short (Fig. 2). There was postaxial hexadactyly of both hand, syndactylous duplication of the right big toe (Fig. 3), and a left clubfoot. Fingernails and toenails appeared normal. Muscular hypotonia was pronounced; seizures developed and the infant died at age 12 days due to respiratory insufficiency. Autopsy was not allowed. Sonography of the skull showed severe internal

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Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

TABLE I. Main Findings in Short-Rib Polydactyly Syndromes*

Manifestations	SRP1	SRP2	SRP3	SRP4	J	EvC
Short ribs	+++	+++	+++	+++	++	+
Platyspondyly	+	+	(+)	+	–	–
Dysplastic pelvis	+	–	+	–	+	+
Ovoid tibiae	–	+	–	–	–	–
Ragged metaphyses	+	–	++	–	–	–
Polydactyly						
Praeaxial	–	+	–	(+)	–	–
Postaxial	+	+	+	(+)	(+)	+
Bowed radii/ulnae	–	(+)	–	+	–	–
Median cleft lip	–	+	–	+	–	–
Holoprosencephaly	–	+	–	+	–	–
Heart defects	+	+	+	+	–	+
Cystic kidneys	+	+	+	+	+	–
Inheritance	AR	AR	AR	AR	AR	AR

*Classification according to Beighton et al. [1992]. SRP1, type Saldino-Noonan; SRP2, type Majewski; SRP3, type Verma-Naumoff; SRP4, type Beemer; J, Jeune syndrome; EvC, Ellis-van Creveld syndrome; AR, Autosomal-recessive.

hydrocephalus, absence of corpus callosum, and hypoplasia of the cerebellum.

Roentgenographically, the thoracic cage was very small due to horizontally-oriented and short ribs. The spine was unremarkable. The pelvis was "dysplastic," with flat acetabula and medial spurs. All long tubular bones were short, but with smooth metaphyses. Radii and ulnae were bowed. The tibiae were short and bowed, with a medial angle. Ossification of the distal femoral epiphyses and of talus and calcaneus was accelerated (Fig. 4).

Case 2, a girl, was born at 39 weeks gestation; birth weight was 3,500 g, length was 51 cm, and OFC was 34 cm. The healthy, nonconsanguineous parents had 2 older normal daughters. The girl was referred because of cyanosis and tachypnea. Clinical examination showed a normal face, a very small thorax, a protruberant abdomen, short limbs, normal hands and feet, and severe muscular hypotonia. There was a 3/6 systolic murmur at the left sternal border. Combined echocardiography and heart catheterization showed levocardia, transposition of great vessels, ventricular septal defect, pulmonic stenosis, and total anomalous pulmonary venous return. In addition, asplenia was detected by ultrasound, with the stomach on the right by X-ray examination. The girl died at age 14 days. Autopsy was not performed. A cytogenetic analysis of pe-

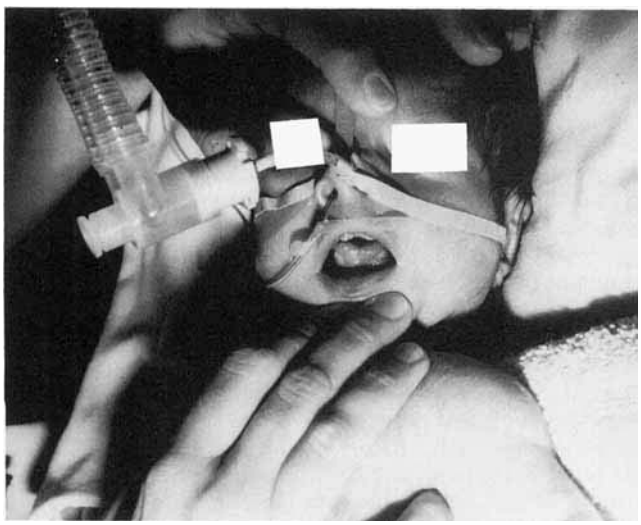

Fig. 1. Face of case 1. Note lobulated tongue.

Fig. 2. Aspect of case 1. Hypertelorism, narrow thorax, postaxial hexadactyly of both hands, hypospadias, bifid scrotum, and short limbs.

Fig. 3. Case 1. Preaxial polysyndactyly.

ripheral blood lymphocytes showed a normal female karyotype (46,XX) at the 450 band level.

Roentgenographically, the thorax was narrow with a bell-shaped configuration. The long bones were short, with widened and ragged metaphyses. The dysplastic pelvis showed a flat acetabulum with medial spurs (Fig. 5). The skull, spine, and hands were normal.

DISCUSSION

Overlapping OFD Syndromes

A brief characterization of the different OFD syndromes is given in Table II. Chitayat et al. [1992] reported on a case with signs of OFD syndromes II–IV and VI; Hingorani et al. [1991] reported on female twins with manifestations of OFD syndromes IV, VI, and the hydrolethalus and Pallister-Hall syndromes; the same overlap was observed by Muenke et al. [1991] in a fetus. Camera et al. [1994] examined a fetus with findings of the OFD syndromes II (Mohr) and VI (Váradi). They considered central polydactyly (V-shaped third metacarpal and duplication of the third finger) to be typical of the OFD syndrome type VI. However, we have observed this kind of polydactyly in cases of Mohr syndrome, as well as in cases with SRP type II [Majewski et al., 1971, and unpublished observations].

Overlapping SRP Syndromes

Bronstein et al. [1994] published a report on a fetus with component manifestations of Jeune syndrome and SRP type III. They discussed compound heterozygosity as a possible cause. Temtamy and McKusick [1978] reported on 2 cases with findings of SRP syndrome type II and Mohr syndrome. At least 9 further similar cases are described [Streichen-Gersdorf et al., 1994]. Meinecke and Hayek [1990] think that these cases are compounds of Mohr and Majewski syndromes,. Martínez-Frías et al. [1993a] reported on 2 unrelated infants with SRPS, whose clinical and radiological findings over lapped all four established types of SRPS. They thought the SRPS to represent a single entity rather than separate entities. Franceschini et al. [1995] reported on a case with signs of SRP syndrome types Majewski, Verma-Naumoff, and Beemer, and Jeune and Mohr syndromes. They discussed the possibility of the existence of contiguous genes for all these syndromes.

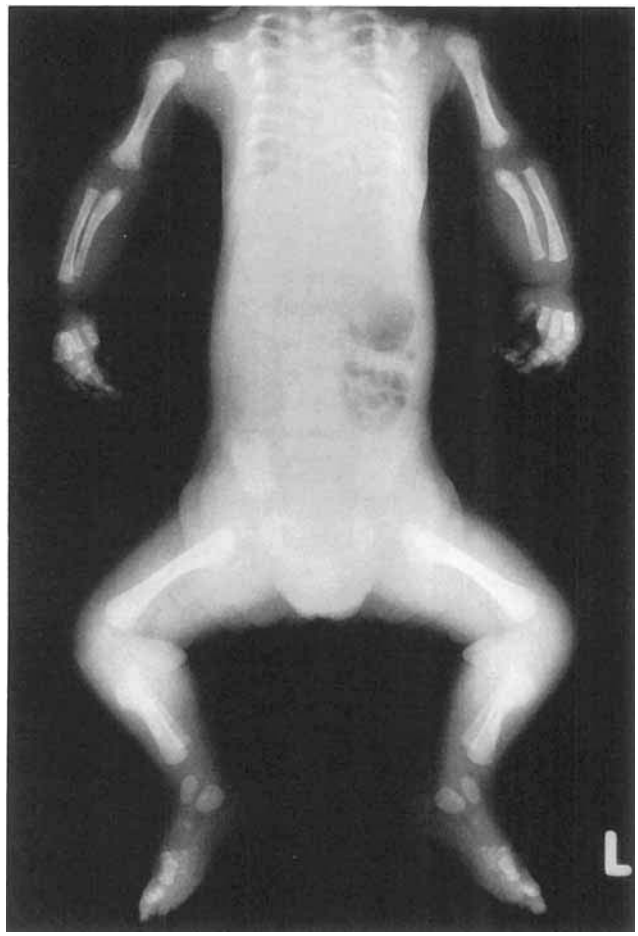

Fig. 4. Babygram of case 1. Short and horizontal ribs, "dysplastic" pelvis, short long bones, and bowed radii, ulnae, and tibiae. Accelerated ossification.

Classification of the Present Cases

The short ribs, the dysplastic pelvis with medial spurs, the short limbs, and the asphyxia of cases 1 and 2 are similar to findings in Jeune syndrome. Postaxial polydactyly, as in the hands of case 1, is infrequently observed in this syndrome. The preaxial polydactyly of one foot as well as the lobulation and the papillomas of the tongue, and the notches of the alveolar ridges, are typical of the OFD syndromes, especially Mohr syndrome, but are also seen in cases with SRPS, type Majewski. The bowed radii and ulnae are typical of SRPS, type Beemer. But since these traits were observed in at least 3 cases with SRPS, type Majewski, and lacking in at least 3 cases with SRPs, type Beemer [Hennekam, 1991], and since Hennekam [1991] observed a pair of sibs with SRPS, type Beemer, one with and one without polydactyly, these traits are not suitable to separate

TABLE II. Major Findings in Oral-Facial-Digital Syndromes*

Manifestations	OFD1	OFD2	OFD3	OFD4	OFD5	OFD6	OFD7	OFD8	OFD9	OFD10?	OFD11?
Mental retardation	±	±	+	±	−	+	±	±	−	−	+
Cleft lip	+	−	−	−	+	+	+	+	+	−	(+)
Oral frenula	+	+	+	+	(+)	+	+	+	+	+	+
Tongue, nodules	+	+	+	+	−	+	+	+	+	−	−
Tongue, lobed	+	+	+	+	−	+	+	+	+	−	(+)
Brachydactyly	+	+	+	+	+	+	+	−	+	−	−
Syndactyly	+	+	+	+	+	+	−	−	+	++	−
Polydactyly, preaxial	−(+)	+	−	+	−	+	−	−	+	+	−
Polydactyly, postaxial	−	+	+	+	+	+	−	+	−	−	+
Reduced tibia	−	−	−	+	−	−	−	+	−	−	−
Brain anomalies	(+)	(+)	−	+	−	+	−	−	−	−	+
Nystagmus	−	−	+	+	−	+	−	−	−	−	−
Other			Myoclonic jerks			Cerebellar hypoplasia	Hydronephrosis	Bifid nose	Retinal anomalies	Oligodactyly Fibular aplasia	Blepharophimosis
Inheritance	XD	AR	AR	AR	AR	AR	AD/XD	XR	AR/XR	?	?

*OFD1, Papillon-Léage-Psaume; OFD2, Mohr-Claussen; OFD3, Sugarman; OFD4, Mohr-Majewski; OFD5, Thurston; OFD6, Váradi; OFD7, Whelan; OFD8, Edwards; OFD9, Gurrieri; OFD10?, Figuera; OFD11?, Gabrielli; (+), rare anomalies; AR, autosomal recessive.

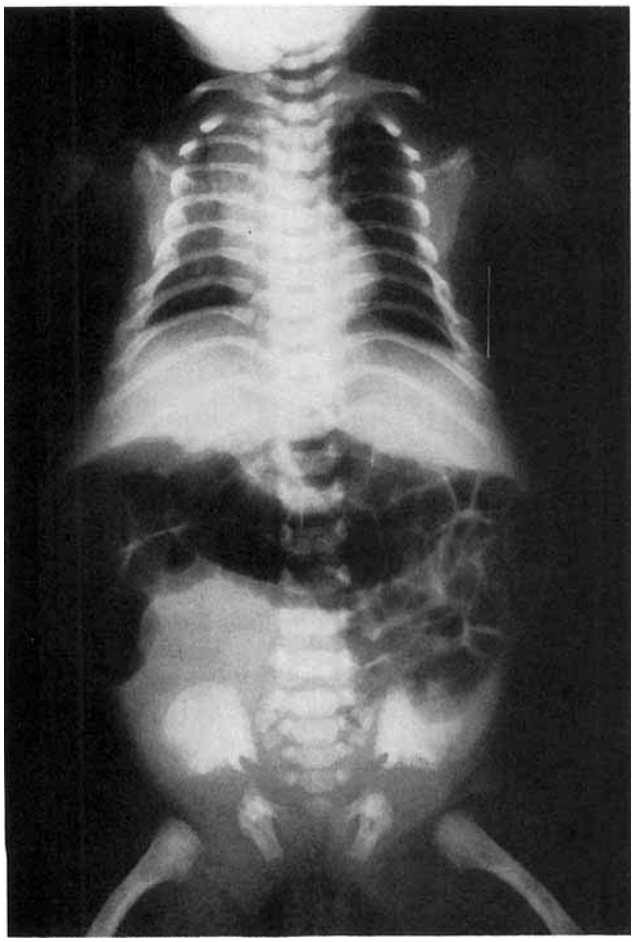

Fig. 5. Babygram of case 2. Short and horizontal ribs, "dysplastic" pelvis, and situs inversus.

types Beemer and Majewski (SRP types IV and II according to the nomenclature of Beighton et al. [1992]. This opinion is further confirmed by the observation of Martínez-Frías et al. [1993b] of one patient with SRPS type II, who had ovoid tibiae (so far observed only in SRPS II and OFD IV syndromes), which in contrast was not present in her affected sib. The absence of ovoid tibiae so far is the only difference between the Beemer and Majewski types of SRPS [Lurie, 1994]. Urioste et al. [1994] observed a pericentric inversion of chromosome 4 in a patient with manifestations overlapping SRPS types II and IV.

Due to normal spine and pelvis, SRPS type II can easily be distinguished from SRPS type III (Verma-Naumoff) and Jeune syndrome. Bowed tibiae are not typical of all entities discussed so far. Accelerated ossification centers are seen in cases with SRPs, type Majewski. Ovoid hypoplasia of the tibiae is typical of SRPS type II and OFD syndrome type IV, which has been termed Mohr-Majewski compound by several authors [Winter and Baraitser, 1991].

Our case 1 is very similar to that reported by Franceschini et al. [1995]. These authors stated that their case had manifestations of Mohr syndrome, Jeune syndrome, and SRP syndromes II–IV. They suggested that all SRP syndromes are a single large nosologic entity. The overlap between SRP and OFD syndromes may be due to deletions of different size within contiguous genes. However, microdeletions are usually either sporadic, or dominantly transmitted. Another possibility for overlap between the SRP and OFD condition(s) may be compound heterozygosity for two of more mutations. In our case 1 we postulate compound heterozygosity for Jeune and Mohr syndromes. The case of Franceschini et al. [1995] could then be explained by heterozygosity due to two different allelic mutations at the same gene locus.

Case 2 had skeletal characteristics of Jeune syndrome. The association of asplenia with cardiovascular malformation and situs inversus is compatible with Ivemark syndrome. Although a few families with Ivemark syndrome are reported [Arnold et al., 1983; Zlotogora et al., 1981], most cases are sporadic; the recurrence risk is thought to be about 5%. In Jeune syndrome, autosomal-recessive inheritance is established. The association of situs inversus was reported by Richardson et al. [1977] in a case with SRPS I, and by Bernstein et al. [1985] and de Sierra et al. [1992] in cases with SRPS III. Spranger and Maroteaux [1990] briefly mentioned 3 cases with SRP syndrome Verma-Naumoff and situs inversus. Brueton et al. [1990] reported on 2 sporadic and unrelated cases. A female infant presented with findings of Jeune syndrome, situs inversus, and renal-hepatic-pancreatic dysplasia, and a male infant presented with symptoms of Ellis-van Creveld syndrome and situs inversus.

There is considerable overlap of findings between SRP subtypes, and between the increasing number of OFD syndromes. This overlap has been explained on the basis of contiguous genes, allelic mutations, or pleiotropy of one gene. On the other hand, there is no phenotypic overlap between Jeune syndrome and Ivemark syndrome. The presence of manifestations of both conditions in the same child (and of the other eight SRP syndromes and Ivemark syndrome traits in the literature) could be explained on the basis of situs inversus and asplenia being components of the laterality sequence as manifestations of some malformation syndromes, e.g., SRP syndromes and Meckel syndrome. Another possibility might be that of compound heterozygosity.

Francomano et al. [1995] have demonstrated linkage of the Ellis-van Creveld (EvC) gene to chromosome areas 4p16. Nagai et al. [1995] suggested an EvC locus is on 12p because of de novo deletion del(12)(p11.21–p12.2) in a boy with radiological signs of Jeune and EvC syndromes. Due to a pericentric inversion of chromosome 4 in a case with findings of SRPS types Majewski and Beemer, Urioste et al. [1994] suggested that the gene for the bone morphogenetic protein-3, which is located in that region, may be involved.

It has been suggested the HOX4 genes on chromosome 2 may be involved in EvC syndrome and the SRPS [OMIM, 1995]. HOX4 genes are expressed in the embryonic limb bud, in the central nervous system, and in the membrane.

We conclude that compound heterozygosity may explain the cases described above and some cases in the literature with overlapping traits of several SRP and OFD syndromes. Molecular studies will show whether allelism or multiple loci are responsible for the overlapping OFD and SRP cases.

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